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ORIGINAL RESEARCH

Ameliorative Effect of Empagliflozin and Linagliptin on Cisplatin-Induced Nephrotoxicity and Cardiotoxicity by Reducing Oxidative Stress

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Introduction: Cisplatin (CP) is a chemotherapeutic agent limited by its toxic effects on the heart and kidneys, resulting in nephrotoxicity and cardiotoxicity. This study investigated the protective effects of the antidiabetic drugs linagliptin (LINA) and empagliflozin (EMPA), alone and in combination, on cisplatin-induced heart and kidney damage in non-diabetic rats.

Methods: Forty-nine rats were randomized into seven groups (n=7 each): control (saline; 10 mL/kg), cisplatin (CP; 10 mg/kg), empagliflozin (EMPA; 10 mg/kg), linagliptin (LINA; 3 mg/kg), and treatment groups (CP+EMPA, CP+LINA, and CP+EMPA+LINA). EMPA and LINA were administered orally for 10 days; CP was administered intraperitoneally on days 1 and 6 after treatment with EMPA, LINA, or both. Renal and cardiac injury biomarkers were measured in the blood. Hearts and kidney tissues from animals were extracted to assess reactive oxygen species (ROS) and malondialdehyde (MDA) concentrations, as well as the activities of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX).

Results: The CP-treated group showed elevated renal, cardiac, and oxidative stress markers. Conversely, the activities of SOD, GPX, and CAT were reduced in the CP-treated groups compared to the control. EMPA, LINA, or combination reduced creatinine, BUN, LDH, CK-MB, troponin I, and ROS levels. LINA showed weaker antioxidant effects in the heart than in the kidney or EMPA.

Conclusion: Our findings suggest that LINA may have a weaker antioxidant effect in the heart than in the kidney or EMPA. Administration of the combinations (LINA+EMPA) affects MDA levels in CP-treated animals, with a significant reduction in the heart and kidney. Individual treatments do not significantly alter MDA levels. However, combined treatment significantly improves SOD, GPX, and CAT activities in the heart and kidney, indicating a superior protective effect, suggesting potential to mitigate CP-induced toxicity.

Keywords: cisplatin, empagliflozin, linagliptin, malondialdehyde, reactive oxygen species, superoxide dismutase, catalase, glutathione peroxidase, cardiorenal toxicity

Introduction

According to the World Health Organization (2023)[1] Cancer accounts for nearly 459,000 deaths in the Eastern Mediterranean region annually.[1] In Saudi Arabia, the incidence of cancer is expected to reach 60,429 by 2040.[2] Cancer poses significant challenges, not only in terms of treatment but also in managing the side effects associated with therapeutic interventions.[2,3] Cisplatin (CP) is a platinum-based chemotherapy medicine categorized as an alkylating agent, a type of cytotoxic medication.[4,5] It is prescribed for several cancer types, including sarcomas and certain carcinomas, such as ovarian, lymphomas, and germ cell cancers.[6] Despite the reliability and efficacy of platinum-based chemotherapeutic agents, the adverse effects of cisplatin, including cardiotoxicity, nephrotoxicity, hepatotoxicity, and hypothyroidism, limit its application.[7,8]

Nephrotoxicity represents the most frequent and clinically significant toxicity associated with CP, affecting up to 30% of patients.[9,10] Research has demonstrated that patients receiving CP treatment are at risk of developing acute kidney injury (AKI), with incidence rates reported between 31% and 68% and a majority of these patients experience a notable

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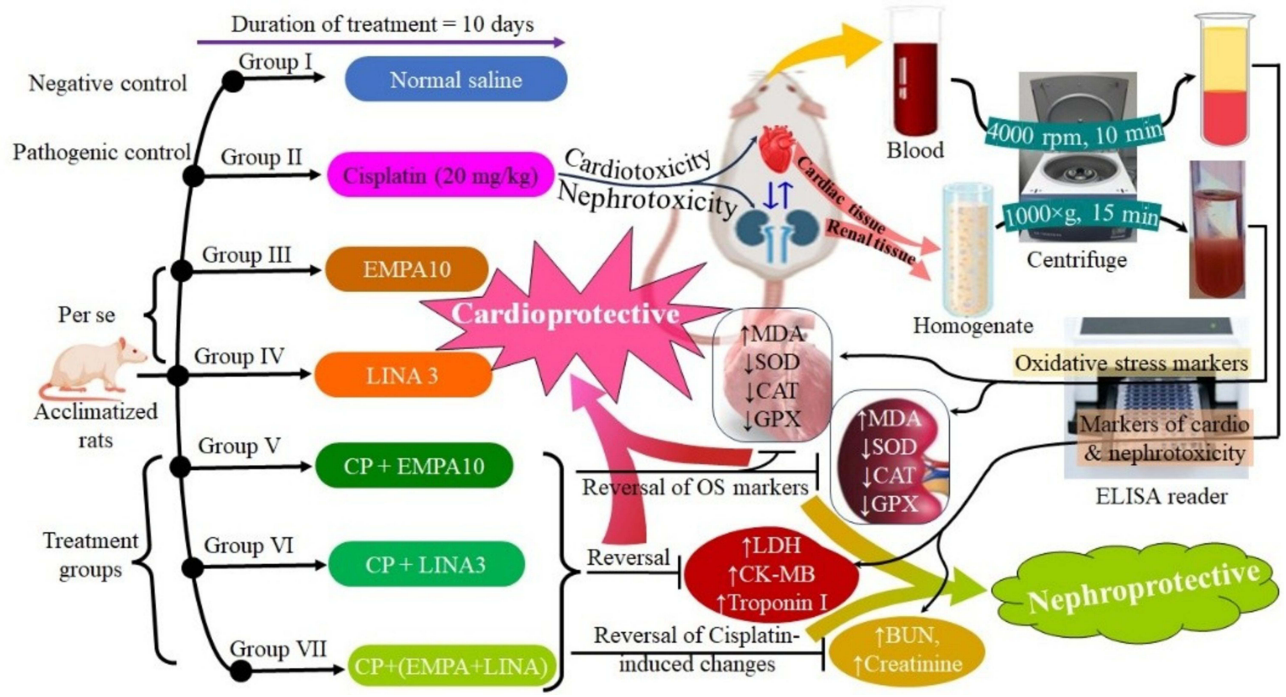
Graphical Abstract



reduction in renal function.[11] CP damages cells in the kidney's proximal tubules, leading to decreased blood flow, inflammation, and eventual cell death.[9] It usually presents as AKI within days of exposure and can lead to immediate and prolonged health issues. Several factors have been identified as being associated with an increased risk of CP-induced renal toxicity, with oxidative stress being the primary factor contributing to the loss of kidney function.[7,12]

CP triggers oxidative stress by generating reactive oxygen species (ROS) and decreasing cellular antioxidant levels, such as glutathione (GSH) and thioredoxin (Trx).[13] This increase in ROS can inflict further harm on DNA, proteins, and lipids, potentially leading to cellular dysfunction and ultimately cell death.[13–15] Research has demonstrated that lipid peroxidation, a consequence of excessive ROS production, is indicative of oxidative stress and is linked to renal toxicity induced by cisplatin.[16] CP negatively impacts antioxidant enzymes, resulting in a marked decrease in renal superoxide dismutase (SOD), glutathione peroxidase, and catalase activities.[17] Additional complications, including proteinuria, enzymuria, glucosuria, and heightened urinary electrolyte excretion, as well as increased plasma creatinine and blood urea nitrogen (BUN) levels, have been documented in both acute and chronic manifestations of cisplatin-induced renal toxicity.[18]

In addition to other toxicities, CP is associated with cardiotoxicity. A retrospective study involving 271 patients who received cisplatin-based chemotherapy reported that 12.9% experienced vascular events.[19] CP may induce indicators for cardiac damage by elevating the levels of specific biomarkers, such as troponin I, creatine kinase (CK-MB), and lactate dehydrogenase (LDH).[20] CP-induced cardiotoxicity includes arrhythmia, atrial fibrillation, angina pectoris, congestive heart failure, myocarditis, and sudden cardiac death.[21] These cardiotoxic events can restrict the chemotherapeutic dosage of CP and increase the long-term incidence of cardiovascular disease.

While the phenomenon of cisplatin-induced cardiac oxidative stress has not been extensively documented, it is plausible that the myocardial stress resulting from cisplatin treatment arises from molecular mechanisms analogous to those identified in the kidney.[9] Research has consistently demonstrated that oxidative stress serves as the fundamental mechanism behind the cardiac toxicity induced by CP.[22] Consequently, oxidative stress is directly implicated in elevating malondialdehyde (MDA) levels, altering antioxidant enzymes such as glutathione, SOD, and catalase, and the

progression of heart failure.[23] In a research study examining isolated rat hearts treated with CP, researchers observed reduced coronary flow and increased cardiac enzyme leakage, both associated with elevated ROS levels[15] and lipid peroxidation.[24]

Moreover, substantial evidence indicates that intracellular stresses, particularly oxidative stress, constitute the primary mechanisms involved.[25] Thus, a promising strategy to address CP-induced nephrotoxicity and cardiotoxicity is to attenuate oxidative stress by deploying antioxidant agents.[26]

Over the past decade, the emergence of oral antidiabetic compounds with novel mechanisms of action has revolutionized the treatment of type 2 diabetes mellitus. These compounds contain sodium glucose cotransporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i), which reduce the occurrence of main adverse cardiac actions, independent of their antihyperglycemic properties.[27–29]

Empagliflozin (EMPA, an SGLT-2 Inhibitor) has demonstrated surprising cardioprotective and renoprotective effects in large clinical trials involving patients with type 2 diabetes mellitus.[30] These benefits extended beyond hyperglycemia suppression, encompassing reductions in kidney and cardiac inflammation, oxidative stress, and mitochondrial dysfunction.[31–33]

DPP-4 inhibitors indirectly diminish myocardial ischemia by preventing the destruction of GLP-1. This allows GLP-1 receptors, plentifully expressed in the nephron and cardiovascular tissues, to become activated.[34] Linagliptin (LINA), a DPP-4i, primarily increases incretin levels, leading to enhanced insulin secretion and the suppression of glucagon release.[35] Recent studies have suggested that linagliptin confers protective benefits to the renal and cardiovascular systems independent of its glucose-lowering actions.[36,37]

The importance of this research is highlighted by the fundamental mechanisms underlying CP-induced injury, including ROS overproduction. These mechanisms differ from those associated with hyperglycemia-mediated damage and occur independently of glycemic status.[38,39] Furthermore, CP-induced cardiorenal toxicity presents a significant clinical challenge for both diabetic and non-diabetic patients undergoing chemotherapy.[40,41] However, no targeted therapies are currently available to prevent these adverse effects.

Evidence suggests that numerous beneficial effects of EMPA and LINA, reduced oxidative stress, and anti-inflammatory properties, are mainly independent of glucose levels.[40,42] These findings suggest that both agents may have therapeutic potential beyond their use in diabetes management. Therefore, our study, unlike prior work that has broadly examined EMPA or LINA in diabetic or metabolic-syndrome contexts, evaluates these agents individually and in combination for their ability to protect against CP–induced cardiorenal injury in non-diabetic animals, a setting in which their effectiveness remains undefined. By testing EMPA and LINA specifically in a CP model, we investigate their glucose-independent protective potential and determine whether combined therapy confers additive benefits, thereby addressing a critical translational gap in mitigating chemotherapy-related oxidative damage.

Materials and Methods

Drugs

Cisplatin (1 mg/mL) was purchased from EBEWE Pharma Ges mbH Nfg.KG (Austria). EMPA (10 mg) and LINA (5 mg) were purchased from Boehringer Ingelheim Pharmaceuticals (Germany). Empagliflozin (EMPA; 10 mg tablets) and linagliptin (LINA; 5 mg tablets) were freshly prepared each day. The required amount of each tablet was finely crushed and dissolved in normal saline to obtain a final concentration of 1 mg/mL for both EMPA and LINA. Adult male rats weighing 200–250 g received the prepared solutions by oral gavage, with the gavage volume adjusted to each rat's body weight to deliver 10 mg/kg for EMPA and 3 mg/kg for LINA. For the combined treatment groups, the calculated volumes of each solution were administered sequentially, resulting in a total daily gavage volume of approximately 2.6–3.25 mL per rat (equivalent to approximately 13 mL/kg).

Animals

A cohort of 49 male rats, each weighing 200–250 grams and 8–10 weeks of age, was obtained from the College of Pharmacy at Qassim University. The rats were housed in propylene cages (four rats per cage) and maintained at 25 ± 2°C

under a 12-h light-dark cycle. They were given unrestricted access to food and water. All procedures were approved by the Animal Care and Use Committee of Qassim University (Ref. no. 23–67-07). All experimental procedures were conducted rigorously in accordance with the ethical guidelines established by Qassim University.

Experimental Design and Drug Administration

The study randomly allocated animals to 7 distinct groups, stratified by baseline body weight, with 7 animals per group (n = 7). The negative control group received an equivalent volume of normal saline (vehicle) by oral gavage once daily for 10 days. The CP group received two intraperitoneal injections of CP (10 mg/kg each) on days 1 and 6 (cumulative dose: 20 mg/kg),[43,44] and also received the normal saline vehicle by oral gavage throughout the 10 days. The EMPA groups received 10 mg/kg of EMPA by oral gavage on day 1 (two hours before CP administration) for 10 days.[45] Similarly, the LINA groups received 3 mg/kg of LINA by oral gavage from day 1 (two hours before CP administration) for the same duration.[44] The CP+EMPA, CP+LINA, and CP+EMPA+LINA groups received two separate doses of CP on day 1 and day 6 at 10 mg/kg/i.p after two hours treated with 10 mg/kg EMPA and 3 mg/kg LINA, which started from day 1 and continued daily received the treatments until day 10, (total duration of the experiments was 10 days). All groups received identical gavage volumes and the same solvent (normal saline), ensuring that any observed pharmacological effects were attributable solely to the administered drugs.

Blood Collection and Plasma Separation

At the end of the 10-day experiments, blood samples were collected by retro-orbital puncture and transferred into heparin-coated tubes. The plasma was then centrifuged for 10 minutes at 4000 rpm at 4°C. The supernatant was collected and transferred into fresh tubes. The plasma was subsequently used for the assessment of renal function, including creatinine (Cat no, RK04308), BUN (Cat no, MBS2611086), and plasma cardiac enzymes, such as CK-MB (Cat no, RK03570), LDH (Cat no, A7625), and troponin I (Cat no, RK04071). These measurements were conducted using a commercially available rat ELISA kit (ABclonal Technology, China) following the manufacturer's protocols. Absorbance measurements for each well were performed at 450 nm using a Microplate Reader (BioTek Instruments, USA).[46]

Preparation of Heart and Kidney Tissue Homogenates

The rats were placed in a glass chamber and anesthetized with $CO2^3$ before being euthanized through decapitation. The heart and kidney tissue samples from seven animals per group were excised and homogenized in 10% (w/v) potassium phosphate buffer (1 g of tissue in 9 mL of 0.1 M potassium phosphate buffer, pH 7.4) on ice. Subsequently, these homogenized tissue samples were centrifuged for 15 minutes at 1000 × g at 4 °C. The supernatant was collected, and the bicinchoninic acid assay (BCA) (Pierce, Waltham, MA, USA) was used to determine the protein content in each sample.[5] Then all the seven samples per group were analyzed for oxidative stress and antioxidant biomarkers, including ROS (Cat no, RK15283), MDA (Cat no, RK15281), SOD (Cat no, RK07054), CAT (Cat no, RK03551), and GPX (Cat no, RK03696), using a rat ELISA kit (ABclonal Technology, China) following the manufacturer's protocols. Absorbance measurements for each well were conducted at 450 nm using a Microplate Reader (BioTek Instruments, USA).

Statistical Analysis

The data analysis was conducted using GraphPad Prism 9 software, which performed a one-way analysis of variance (ANOVA) based on the data distribution. Subsequently, the Tukey-Kramer post hoc test was employed to facilitate multiple comparisons. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

The Effect of LINA and EMPA Alone, and in Combination with CP, on Renal Biomarkers

The animals injected with CP showed a significantly higher creatinine level than the control group (Figure 1A). In contrast, a significant reduction in creatinine levels was detected in all other treated animals (CP+LINA, CP+EMPA, and CP+LINA+EMPA) compared to the CP groups (Figure 1A). The BUN level was significantly higher in the CP-treated animals than in the control group (Figure 1B). Moreover, it was significantly decreased in treated animals (Figure 1B).

The Effect of LINA and EMPA Alone, and in Combination with CP, on Cardiac Biomarkers

Cardiac biomarker evaluation revealed a significantly elevated CK-MB level in the animals with CP compared to the control groups. Animal-treated groups (CP+LINA, CP+EMPA, and CP+LINA+EMPA) receiving therapy exhibited a significantly decreased CK-MB level compared to CP-treated rats (Figure 2A). Furthermore, troponin I levels were significantly elevated in the CP-treated animals compared to the control groups and significantly decreased in the treated animals compared to the CP-treated rats (Figure 2B).

The Effect of LINA and EMPA Alone and in Combination with CP, on Lactate Dehydrogenase (LDH)

The LDH level was significantly elevated in the CP-treated rats in comparison to the control group (Figure 3). In contrast, a significant decline in LDH levels was detected in the treated rats (CP+LINA, CP+EMPA, and CP+LINA+EMPA) compared to the CP-treated animals (Figure 3).

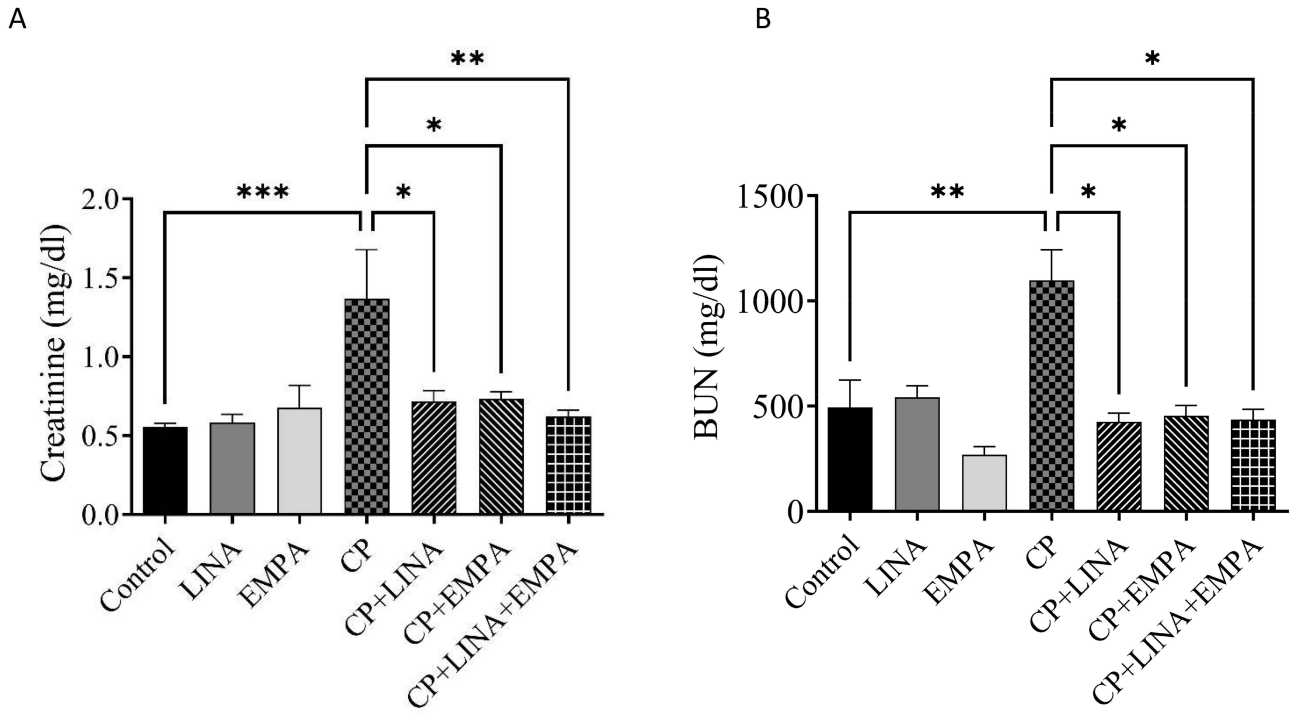


Figure 1 The influence of LINA and EMPA alone and in combination with CP, on renal creatinine (**A**) and BUN (**B**) biomarkers. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test. Asterisks indicate the level of statistical significance of the multiple comparison test; *p < 0.05, **p < 0.01, and ***p < 0.001 compared to the control/CP-treated animals.

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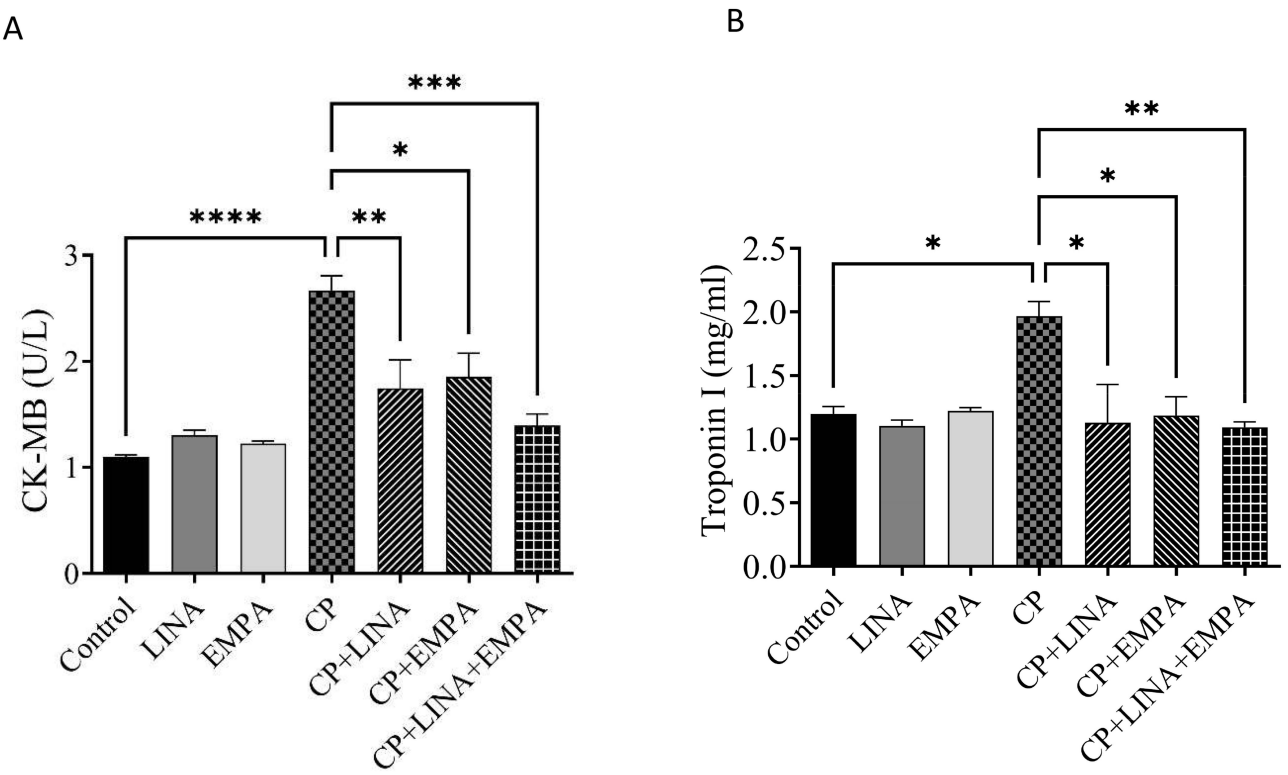

Figure 2 The influence of LINA and EMPA alone and in combination with CP on cardiac Creatine Kinase (**A**) and Troponin I (**B**) biomarkers. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test; *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 in comparison with the control / CP-treated animals.

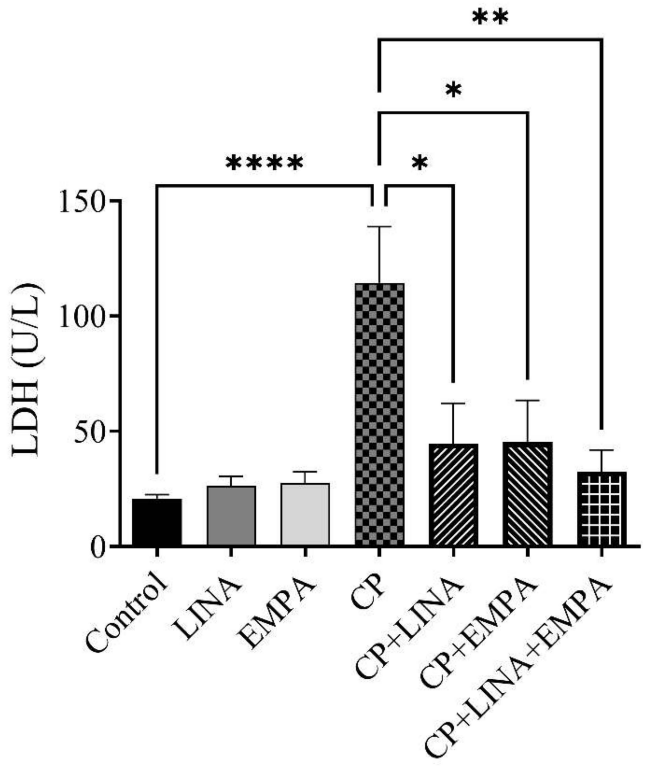

Figure 3 The impact of LINA and EMPA alone and in combination with CP on LDH levels. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test; *p < 0.05, **p < 0.01, and ****p < 0.0001 in comparison to the control / CP-treated animals.

The Effect of LINA and EMPA Alone and in Combination with CP on Oxidative Stress Markers in the Rat Heart and Kidney

Superoxide Dismutase

The SOD activity in the cardiac tissues exhibited a significant drop in the CP-injected animals and CP+LINA compared to the control groups (Figure 4A). Alternatively, a considerable increase in SOD activity was observed in the CP+EMPA and CP+LINA+EMPA-treated animals compared to the CP groups (Figure 4A). In kidney tissue, SOD activity was significantly reduced in the CP groups and CP+LINA compared with the control group. In contrast, the CP+EMPA and CP+LINA+EMPA groups exhibited a significant elevation in SOD expression compared to the CP-treated animals. In contrast, the CP+LINA group showed no difference from the CP group in the kidney (Figure 4B).

Catalase

The CAT activity was significantly lower in the CP and CP+LINA groups than in the control group (Figure 5A). In contrast, the CAT activity was significantly elevated in the CP+EMPA and CP+LINA+EMPA-treated rats than in the CP group. Kidney CAT activity in the CP showed a significant decline compared with the control (Figure 5B). In contrast, kidney CAT activity was significantly increased in the CP+LINA, CP+EMPA, and CP+LINA+EMPA-treated rats compared to the CP group (Figure 5B).

Glutathione Peroxidase

GPX activity in cardiac tissues was significantly reduced in CP- and CP+LINA-treated animals compared with the control group (Figure 6A). Nevertheless, the cardiac GPX activity in the CP+EMPA and CP+LINA+EMPA groups was significantly increased compared to the CP-injected animals. GPX activity in the kidneys was significantly lower in the CP-injected animals than in the control group. Nevertheless, this activity was significantly increased in the CP+LINA, CP +EMPA, and CP+LINA+EMPA groups compared with the CP group (Figure 6B).

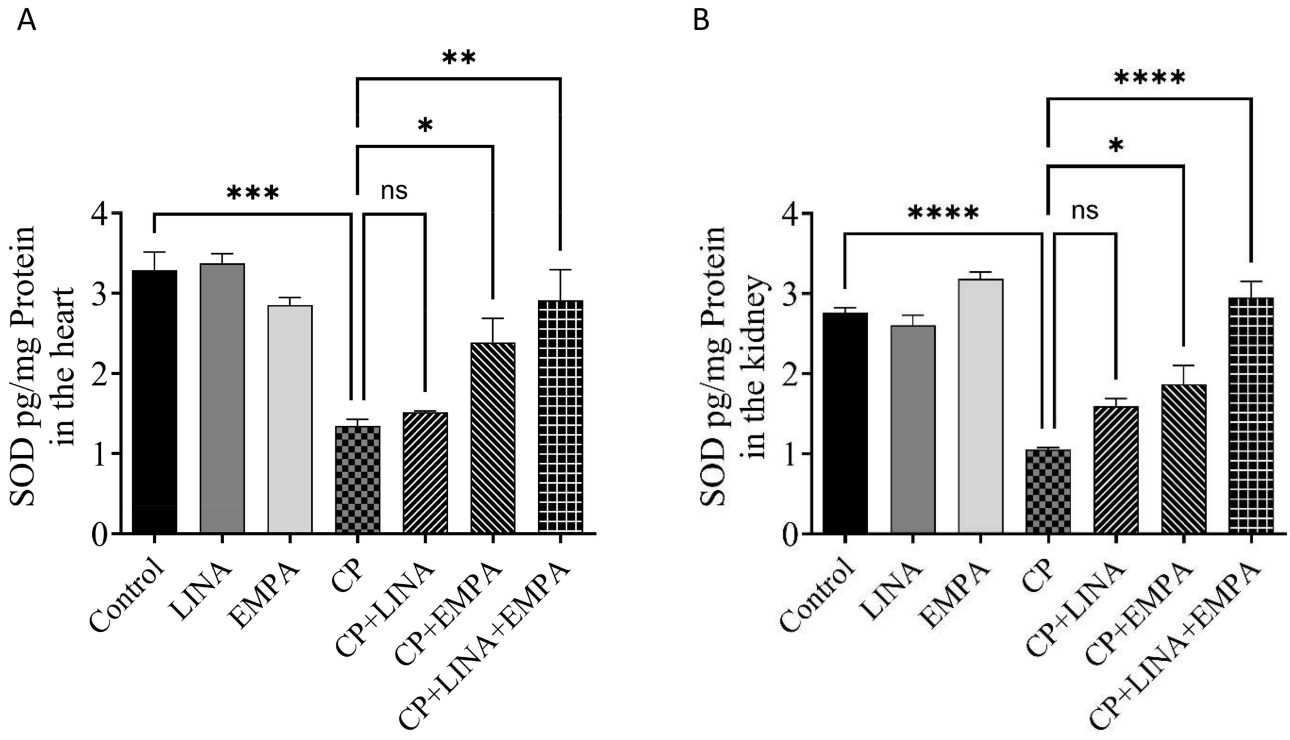

Figure 4 The impact of LINA and EMPA alone and in combination with CP, on SOD activity. (**A**) Effect of LINA and EMPA, alone, and in combination with the CP group, on SOD activity in the heart. (**B**) Effect of LINA and EMPA alone and in combination with CP on SOD activity in the kidney. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by the Tukey-Kramer post hoc test; *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 in comparison to the control/CP-treated rats.

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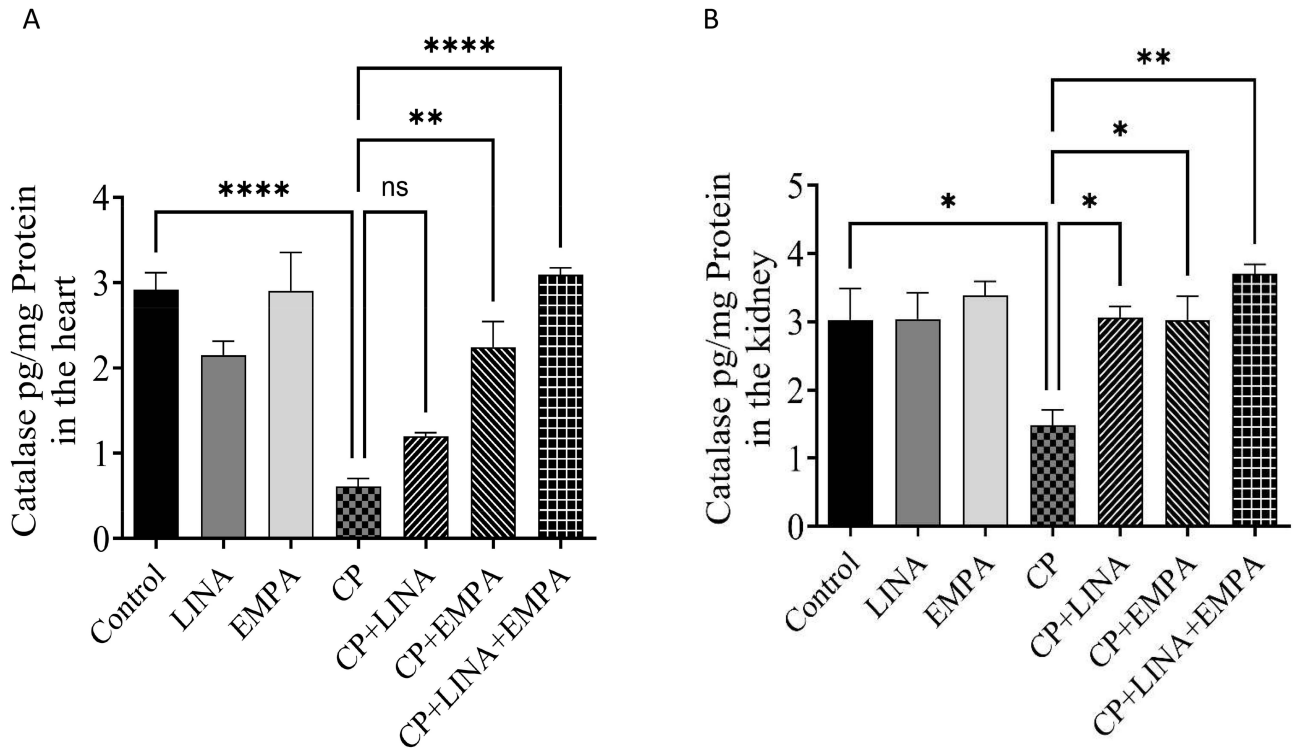

Figure 5 The impact of LINA and EMPA alone and in combination with CP on CAT activity. (**A**)The effect of LINA and EMPA, alone, and in combination with CP, on CAT activity in the heart. (**B**). Effect of LINA and EMPA alone and in combination with CP on CAT in the kidney. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test.; *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 in comparison to control / CP-treated animals.

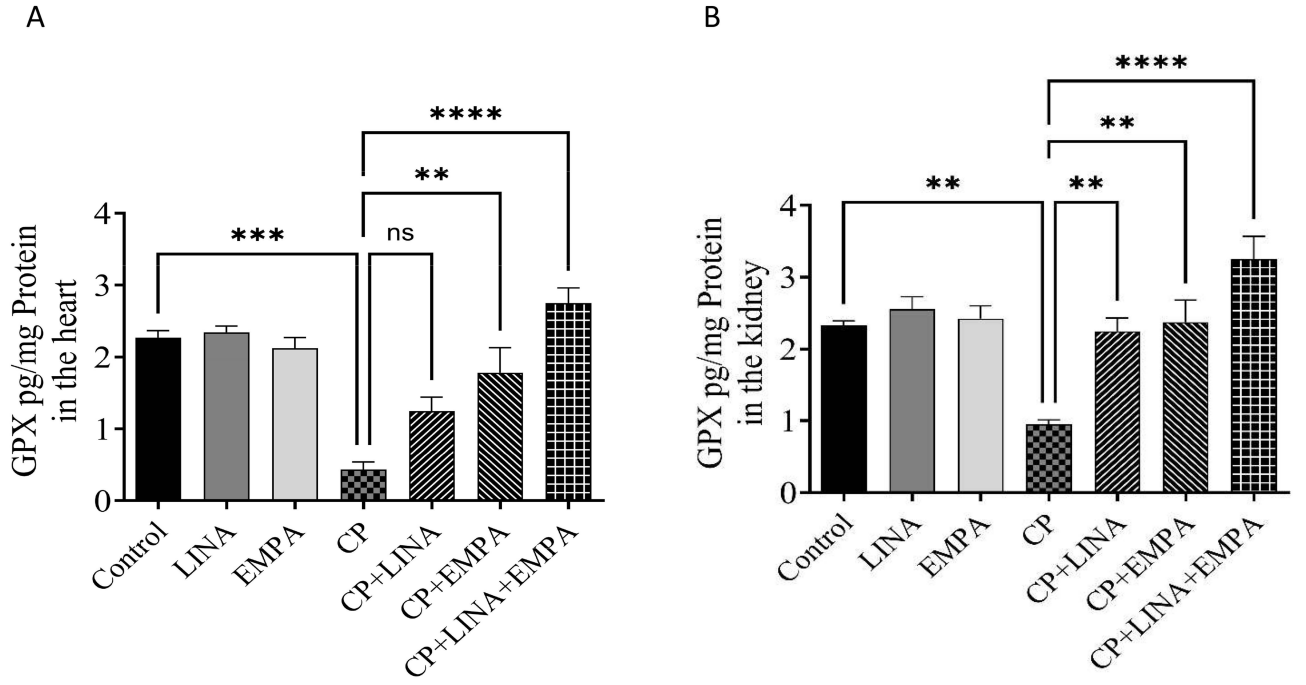

Figure 6 The influence of LINA and EMPA, alone, and in combination with CP, on GPX activity. (**A**) Effect of LINA and EMPA, alone, and in combination with CP, on GPX in the heart. (**B**) Effect of LINA and EMPA alone and in combination with CP on GPX in the kidney. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test. **p < 0.01, ***p < 0.001 and ****p < 0.0001 compared to the control/ CP treated group.

Malondialdehyde

The MDA levels were significantly higher in the CP-injected animals than in the control rats (Figure 7A). At the same time, the CP+LINA and CP+EMPA groups showed a reduction that was not statistically significant compared with the CP group. However, the combined CP+LINA+EMPA group demonstrated a significant reduction compared to the treatment alone or with the CP group. The kidney MDA level was significantly elevated in the CP-injected rats compared to the control group. In addition, the CP+LINA and CP+EMPA groups showed a reduction that was not statistically significant compared with the CP group. On the other hand, a considerable drop in MDA level was observed in CP +LINA+EMPA-treated animals compared to the treatment alone and the CP group (Figure 7B).

Reactive Oxygen Species

The ROS level in cardiac tissues was significantly elevated in the CP-treated animals compared to the control group (Figure 8A). However, ROS levels were significantly reduced in CP+LINA, CP+EMPA, and, most prominently, in the combination group compared with CP-treated animals. Kidney ROS levels were significantly elevated in the CP-treated animals compared to the control group. Conversely, a significant drop in ROS levels was detected in CP+LINA, CP +EMPA, and, most prominently, in the combination group compared with CP-treated animals (Figure 8B).

Discussion

Previous research has established the efficacy of cisplatin (CP) as a critical chemotherapeutic agent, notwithstanding its documented adverse effects.[5,47] Moreover, clinical hypotheses propose that oxidative stress is linked to the structural and functional abnormalities that are evident in renal injury and heart failure.[7] Thus, it is essential to identify an adjuvant therapy to mitigate the nephrotoxic and cardiotoxic effects associated with CP.[7] The current research study aimed to explore the potential ameliorative effects of the SGLT2 inhibitor Empagliflozin (EMPA) and the DPP4 inhibitor

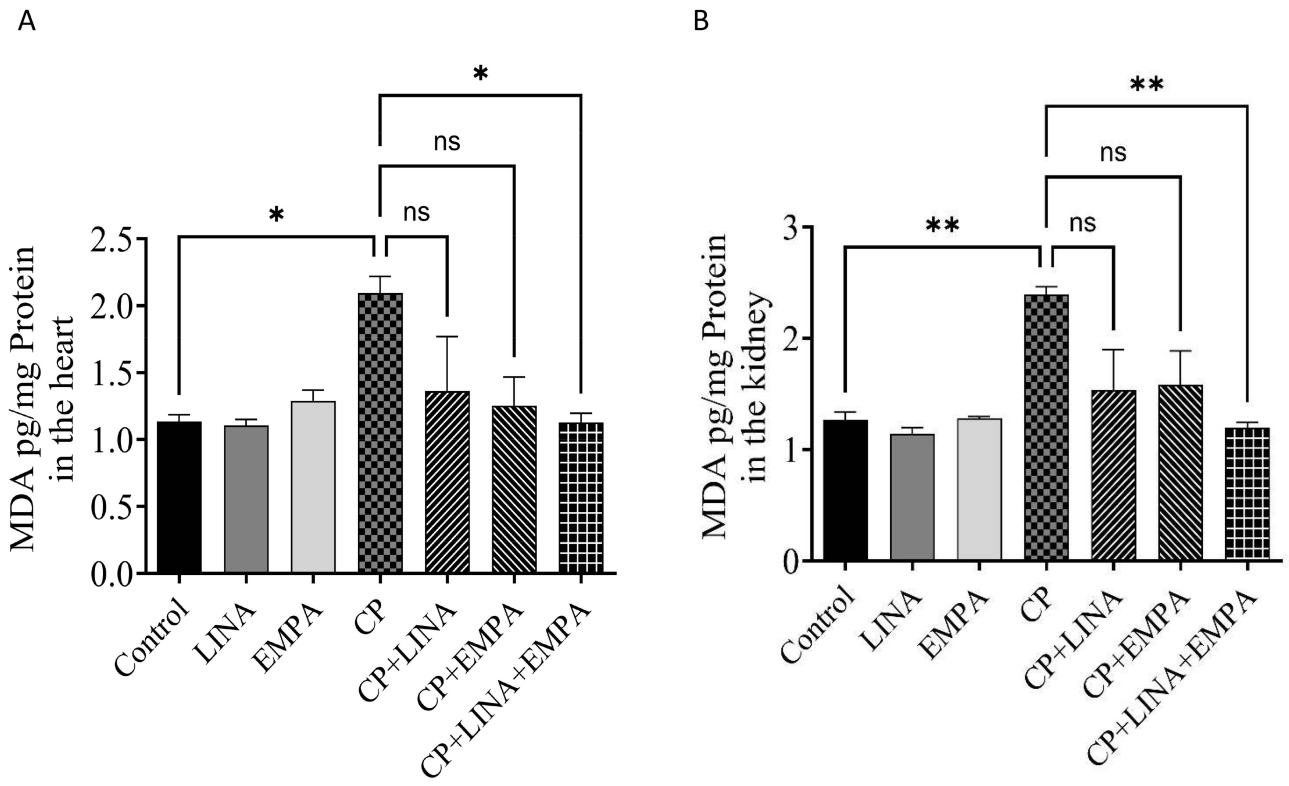

Figure 7 The impact of LINA and EMPA alone and in combination with CP on MDA level. (**A**) Effect of LINA and EMPA alone and in combination with CP, on MDA level in the heart. (**B**) Effect of LINA and EMPA alone and in combination with CP, on MDA level in the kidney. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test; *p < 0.05 and **p < 0.01 compared to the control / CP-treated group.

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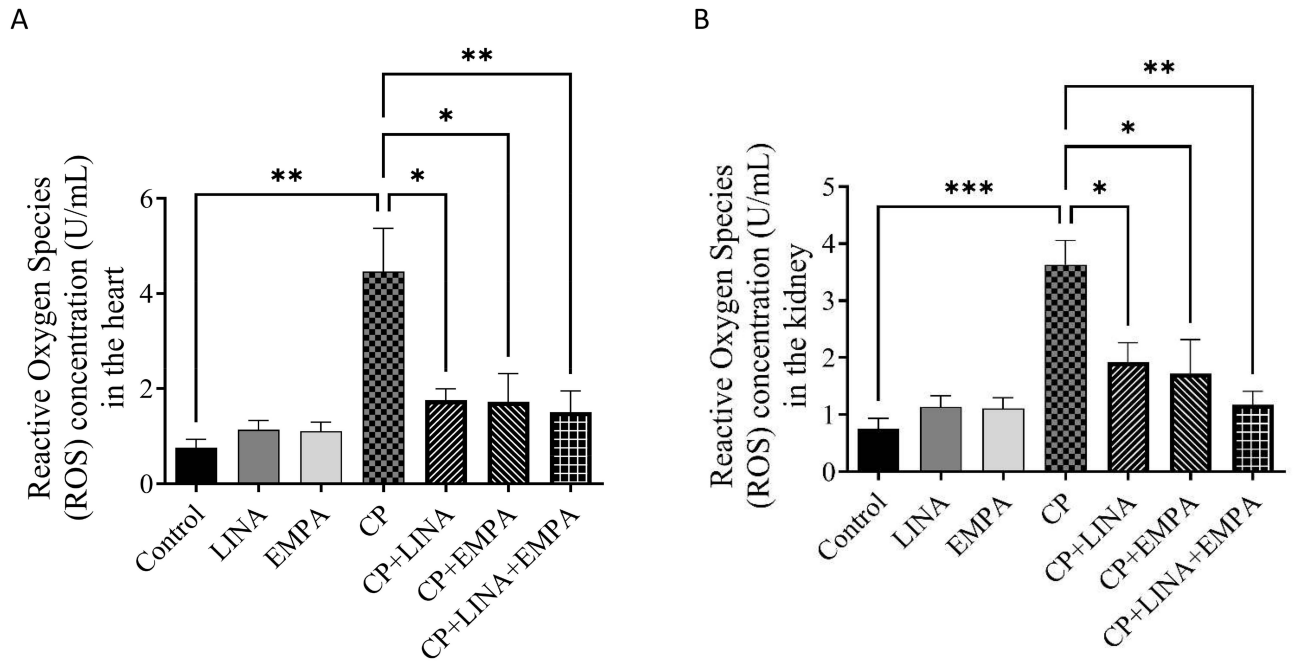

Figure 8 The impact of LINA and EMPA alone and in combination with CP on ROS levels. (**A**) Effect of LINA and EMPA alone, and in combination with CP, on ROS level in the heart (**B**). Effect of LINA and EMPA alone and in combination with CP on ROS levels in the kidney. The results are expressed as mean ± SEM (n=7). Data analysis was performed using one-way ANOVA followed by Tukey-Kramer post hoc test; *p < 0.05, **p < 0.01, and ***p < 0.001 in comparison to the control / CP-treated rats.

Linagliptin (LINA), both antidiabetic drugs, on cardiorenal injury induced by CP, and to elucidate the molecular mechanisms underlying CP-induced toxicity.

Nephrotoxicity caused by CP is characterized by deterioration in kidney function, resulting in elevated plasma creatinine and BUN levels.[48] The present study demonstrates that creatinine and BUN levels were significantly elevated in CP-treated rats compared with untreated controls. The results indicate that CP administration leads to nephrotoxicity. Our findings are aligned with a previous study utilizing an animal model of cisplatin-induced nephrotoxicity, which observed significantly elevated levels of several plasma parameters, including BUN and creatinine, in rats treated with cisplatin.[49,50] Interestingly, concurrent administration of LINA and EMPA, or the combination of LINA, EMPA, and CP, effectively restores the elevated creatinine and BUN levels induced by CP to normal levels, comparable to those observed in the control group.

Cisplatin is known to compromise the integrity of cell membranes in the heart, which in turn facilitates the release of intracellular proteins such as cardiac Troponin I, CK-MB, and LDH.[47,51,52] Previous research has demonstrated a significant increase in CK-MB and troponin I levels following CP administration, compared with control groups.[22] In our study, we observed significantly elevated levels of cardiac Troponin I, CK-MB, and LDH in rats administered CP compared with the control group, indicating myocardial injury. The elevation in cardiac Troponin I, CK-MB, and LDH induced by CP was mitigated by co-treatment with LINA, EMPA, or the combination of LINA+EMPA, compared with CP-treated rats. Therefore, our study suggests that EMPA and LINA, alone or in combination, may provide a promising therapeutic agent for preventing cardiorenal toxicity induced by CP. However, the combined co-treatment has a more significant effect than the individual treatments.

LINA and EMPA treatment significantly attenuated these biochemical changes, suggesting that they effectively counteract CP-induced heart and kidney injury. This finding aligns with those reported in a previous study,[53] which observed that EMPA considerably reduced nephrotoxicity caused by methotrexate (MTX).[53] The rats in the MTX+EMPA group demonstrated a statistically significant decrease ($p < 0.001$) in plasma creatinine and urea levels compared to those in the MTX-treated group. Furthermore, a research study reported that EMPA ameliorated alcohol-induced cardiotoxicity in mice, with a 1.46-fold and 1.49-fold reduction in plasma troponin I and CK-MB levels, respectively.[54] This finding aligns with previous documentation that LINA offered protection against tacrolimus-induced renal injury, with LINA co-

treatment remarkably reducing Scr and the BUN/Scr ratio to 35% and 28%, respectively.[55] A model of isoprenaline-induced myocardial infarction in rats was developed, and it was found that LINA reduced elevated plasma cardiac troponin I levels caused by isoprenaline administration.[56] Finally, a study reported that LINA treatment reduced CK-MB and LDH levels in diabetic rats, highlighting its role in tissue protection.[57]

Recent research has shown that oxidative stress emerges following cisplatin infusion.[58] CP has been demonstrated to induce renal and cardiac toxicity through the enhancement of oxidative stress through increased free oxygen radical production.[58] The principal mechanism underlying kidney injury is oxidative stress, as CP contains chloride ions that undergo hydrolysis, releasing hydroxyl radicals. The elevation in ROS formation leads to lipid peroxidation and an increase in MDA levels.[59] In instances of oxidative tissue damage, an increase in MDA levels and a reduction in the endogenous enzymatic antioxidants, including SOD, GPX, and catalase, are observed.[60] The enzymatic defense provided by cellular antioxidants plays a crucial role in mitigating the harmful effects of oxidative stress caused by free radicals, by converting superoxide anion to hydrogen peroxide (H_2O_2) by SOD, and then converting hydrogen peroxide to water by GPx and catalase.[61]

In this study, EMPA treatment alone significantly mitigated CP-induced oxidative damage, as evidenced by the restoration of renal and cardiac SOD, CAT, and GPX activities. EMPA reduced cardiac and renal MDA levels, but no statistically significant difference was observed compared with CP-treated animals. At the same time, EMPA treatment alone resulted in a substantial reduction in ROS levels compared with the CP group. Prior clinical investigations have shown that EMPA maintains kidney-protective efficacy even with a diminished Glomerular Filtration Rate.[34,35] EMPA has received approval for the treatment of heart failure in individuals with and without diabetes.[62] In addition to regulating hyperglycemia, SGLT-2i also protects the kidneys and heart by reducing oxidative stress, inflammatory processes, sympathetic nerve activity, and autophagy.[63,64] EMPA lowered oxidative stress biomarkers.[64] In the cardiac tissue of diabetic mice, a reduction in NOX4 expression occurs as a consequence of the activation of the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signaling cascade.[42] Therefore, our findings and those of previous studies confirm that the potential therapeutic effectiveness of SGLT-2 may be used to treat non-diabetic renal disorders [66] and mitigate cardiovascular incidents, especially following chemotherapy, such as cisplatin.[65]

LINA is recognized for its renoprotective properties. Notably, it is the only medication in its class primarily excreted through non-renal pathways, eliminating the need for dose adjustments in patients with chronic renal disease.[66,67] Previous studies have suggested that LINA may offer nephroprotective benefits against CP treatment, although the precise mechanisms of damage and protection remain incompletely understood. Our research examines the impact of CP on oxidative stress, as measured by oxidative stress biomarkers and endogenous enzymatic antioxidants, including SOD, GPX, and catalase. Unlike other drugs in this category, LINA features a xanthine backbone and has the potential to inhibit xanthine oxidase, an enzyme crucial to purine metabolism that produces ROS.[68] LINA mitigated ROS production by activating the nuclear factor erythroid-2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway.[69] Our investigation revealed that LINA treatment alone did not demonstrate a statistically significant enhancement in cardiac SOD, GPX, and CAT levels. LINA also shows a significant decrease in renal ROS levels compared with CP-treated animals. Although cardiac MDA levels decreased, the difference did not reach statistical significance. Conversely, cardiac ROS levels were significantly lower than those in CP-treated animals.

This study indicated that LINA may have weaker antioxidant action than EMPA. Moreover, LINA showed weaker antioxidant effects in the heart than in the kidney following cisplatin exposure. Previous studies show LINA has a greater renal tissue exposure and interacts with a higher density of DPP-4 enzymes in proximal tubular cells, enabling more efficient inhibition and downstream activation of antioxidant pathways.[40,55,70] In contrast, the cardioprotective actions of LINA appear to rely mainly on anti-inflammatory, anti-fibrotic, and metabolic mechanisms, with relatively modest or non-significant improvements in classical myocardial antioxidant enzymes.[71–73] Taken together, the available evidence supports our observation that LINA induces a more robust renal antioxidant response than cardiac tissue, accounting for the greater improvement in renal oxidative biomarkers compared with cardiac biomarkers in the current cisplatin model. Additionally, not all research supports the hypothesis that LINA or EMPA can exert antioxidative effects as a mechanism for cardioprotection.[74] Conversely, a prior study demonstrated a significant improvement in EMPA's efficacy against cardiotoxicity through non-antioxidant pathways.[75]

This research showed that the combination of EMPA and LINA significantly decreased antioxidant biomarkers (SOD, GPX, and CAT) in heart and kidney tissues and increased cardiac and renal MDA and ROS levels in CP-treated rats.[76] Furthermore, elevation of ROS depletes antioxidant enzyme levels, ultimately disrupting the cellular balance between oxidation and antioxidants, and precipitating intracellular oxidative stress.[77,78] In addition, our findings revealed that oral administration of the combination (EMPA+LINA) improved renal and cardiac parameters following CP treatment. This improvement is reflected in restoring the levels of oxidative stress biomarkers ROS and MDA, as well as increasing the levels of SOD, GPx, and catalase. This result has increasingly recognized that SGLT-2 and DPP-4 inhibitors offer tissue-protective benefits in addition to their systemic glucose-lowering capabilities.

Our data suggest that EMPA or LINA alone had weaker effects than the combination. Therefore, the combined use may exhibit greater efficacy in alleviating cardiorenal injury induced by CP. The enhanced protective effect of the EMPA and LINA combination against cisplatin-induced cardiorenal injury may be attributed to their complementary antioxidant and cytoprotective pathways. EMPA activates the Nrf2/ARE and Nrf2/HO-1 signaling cascades, suppresses NADPH oxidase-derived ROS formation, and mitigates fibrosis and inflammation in both cardiac and renal tissues.[42] Conversely, LINA confers renoprotection by partially inhibiting xanthine oxidase and robustly activating Nrf2/HO-1, thereby increasing the activities of SOD, GPx, and CAT.[40,55] Additionally, LINA enhances mitochondrial quality control by engaging SIRT3/PGC-1α and PINK1/Parkin-mediated mitophagy, mechanisms that are highly responsive in renal tissue.[79] Given that cisplatin suppresses Nrf2 signaling and promotes excessive oxidative stress,[38] our finding that the activation of antioxidant pathways by EMPA and the reduction of ROS generation by LINA likely act synergistically. This dual pathway modulation elucidates the antioxidant and potential protective effects observed with the combination compared to individual treatments.

The study exhibits both limitations and strengths. A significant strength is the consistent application of strain, age group, and gender. Moreover, while numerous studies have demonstrated LINA's cardioprotective effects, this study is the first to evaluate oxidative markers of these effects in non-diabetic rats treated with CP. Additionally, this study is unique in its assessment of the ameliorative effect of a combined LINA and EMPA treatment on cardiorenal injury induced by CP. The study's limitations include the lack of histological validation of cardiac and kidney damage due to limited laboratory resources. However, future research should incorporate histological assessments of cardiac and kidney damage, as well as pathological changes in these organs, to verify and extend our findings. Furthermore, additional studies are necessary to elucidate the mechanisms of cardiotoxicity and nephrotoxicity by examining biomarkers of inflammation and apoptosis.

In conclusion, this study revealed that the combination of improved cardiorenal function and reduced oxidative stress was seen more effectively than monotherapy in cisplatin-treated rats. These findings indicate the ameliorative effects of these drugs on cisplatin-induced cardiorenal toxicity. Consequently, LINA and EMPA combined have the potential to mitigate cardiorenal damage associated with cisplatin treatment. Further research is necessary to investigate these effects in more detail and comprehensively elucidate the underlying mechanisms.

Institutional Review Board Statement

The ethics and protocol of this research were approved (23-67-07) by the Committee of Research Ethics, Deanship of Graduate Studies and Scientific Research, Qassim University.

Data Sharing Statement

Data will be available from the corresponding author upon request.

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This paper is based on the thesis of Malak S. Alharbi. It has been published on the institutional website.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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